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EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT PAPER NUMBER

1634

DATE MAILED: 09/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/037,469	Applicant(s) WARD ET AL.	
	Examiner Jeffrey Fredman	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on ____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-59 is/are pending in the application.

4a) Of the above claim(s) ____ is/are withdrawn from consideration.

5) ☐ Claim(s) ____ is/are allowed.

6) ☒ Claim(s) 1-59 is/are rejected.

7) ☐ Claim(s) ____ is/are objected to.

8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.

4) ☐ Interview Summary (PTO-413) Paper No(s). ____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claims 1-3, 8, 9 and 59 are rejected under 35 U.S.C. 102(e) as being anticipated by Tyagi et al (U.S. Patent 6,277,607).

Tyagi teaches a method of detecting target nucleic acid sequences (see abstract), the method comprising:

(a) bringing into contact one or more target samples and one or more structured probes (see column 9, lines 12-56, figure 1 and column 11, example 1), and incubating under conditions that promote hybridization between target nucleic acid sequences in the target samples and the structured probes (see column 9, line 57 to column 10, line 8), wherein each structured probe is bifunctional (see figure 1), wherein one function is as a probe to a target nucleic acid sequence (see figure 1 and column 8, lines 39-67 and column 11, example 1) and the other function is a detection function, wherein the detection function is not possible unless the probe hybridizes to the target nucleic acid sequence (see figure 1 and column 11, example 1)

wherein each structured probe has a first end and a second end (see figure 1), wherein each structured probe comprises at least two complementary portions, a target probe portion (see figure 1, column 9, and column 11, example 1) and a detection portion (see figure 1 and column 11, example 1), wherein the two or more complementary portions comprise a first complementary portion and a second complementary portion, wherein two or more of the complementary portions form a duplex region (see figure 1) wherein formation of the duplex region forms a loop (see figure 1), wherein at least a portion of the target probe portion is in the loop (see figure 1 and column 5, lines 10-35), wherein hybridization of the target probe portion to the target nucleic acid sequence disrupts the duplex region (see figure 1 and column 5, lines 22-24),

(b) detecting the structured probes (see column 11, example 1 and figure 2),

wherein prior to detection, the structured probes are treated to alter or eliminate unhybridized probes wherein only probes with intact duplex regions are altered or eliminated by treatment of the structured probes, wherein altered and eliminated probes are not detected (see column 7, line 67 to column 8, lines 7, where detection can be performed by polyacrylamide gel electrophoresis, which will separate hybridized probes from unhybridized probes).

With regard to claim 2, 8 and 9, Tyagi teaches that the probe may have a single stranded overhang (see column 6, line 3) wherein the probes are treated with the amplification (see column 5, lines 23-25).

With regard to claim 3, as above, Tyagi teaches that the probe may have a single strand overhang (see column 6, line 3) and the functional limitation that the probe cannot prime is met by the 5' end, since the 5' end cannot prime amplification by itself.

With regard to claim 59, Tyagi teaches that the target probe will not hybridize to a mismatched nucleic acid sequence (see column 5, lines 45-55).

3. Claims 1-3, 5-9, 20-28, 30-34 and 59 are rejected under 35 U.S.C. 102(e) as being anticipated by Tyagi et al (U.S. Patent 5,925,517).

Tyagi teaches a method of detecting target nucleic acid sequences (see abstract), the method comprising:

(a) bringing into contact one or more target samples and one or more structured probes (see columns 31-32, Example VI), and incubating under conditions that promote hybridization between target nucleic acid sequences in the target samples and the structured probes (see column 32, lines 7-13 and column 15, lines 1-23), wherein each structured probe is bifunctional (see figures 3 and 4), wherein one function is as a probe to a target nucleic acid sequence (see figures 3 and 4, and column 32, lines 30-40) and the other function is a detection function, wherein the detection function is not possible unless the probe hybridizes to the target nucleic acid sequence (see figures 3 and 4 and lines 30-40 and column 5, lines 27-67)

wherein each structured probe has a first end and a second end (see figures 3 and 4), wherein each structured probe comprises at least two complementary portions, a target probe portion (see figures 3 and 4 and column 5, lines 27-43 and columns 9-11) and a detection portion (see figures 3 and 4 and column 5, lines 27-43 and columns 9-

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11), wherein the two or more complementary portions comprise a first complementary portion and a second complementary portion, wherein two or more of the complementary portions form a duplex region (see figures 3 and 4) wherein formation of the duplex region forms a loop (see figures 3 and 4), wherein at least a portion of the target probe portion is in the loop (see figures 3 and 4 and column 5, lines 27-43 and columns 9-11), wherein hybridization of the target probe portion to the target nucleic acid sequence disrupts the duplex region (see figures 3 and 4 and column 5, lines 27-43 and columns 9-11 and column 32, lines 30-40),

(b) detecting the structured probes (see column 32, lines 20-65),

wherein prior to detection, the structured probes are treated to alter or eliminate unhybridized probes wherein only probes with intact duplex regions are altered or eliminated by treatment of the structured probes, wherein altered and eliminated probes are not detected (see column 21, lines 51-55, where detection can be performed by polyacrylamide gel electrophoresis, which will separate hybridized probes from unhybridized probes). Further, Tyagi teaches the use of low stringency washing of solid supports such as Southern blots (see column 21, line 59 to column 22, line 13).

With regard to claim 2, 8 and 9, Tyagi teaches that the probe may have a single stranded overhang (see column 19, lines 13-15) wherein the probes are treated with the amplification (see column 20, lines 40-56).

With regard to claim 3, as above, Tyagi teaches that the probe may have a single strand overhang (see column 19, lines 13-15) and the functional limitation that the probe cannot prime is met by the 5' end, since the 5' end cannot prime amplification by itself.

With regard to claims 5-7, 30-34, Tyagi teaches formation of probes tethered to a solid support (see column 37, lines 15-40 and figure 10).

With regard to claim 20, Tyagi teaches the use of low stringency washing of solid supports such as Southern blots (see column 21, line 59 to column 22, line 13).

With regard to claims 21-26, and 28, Tyagi teaches that the parameters of distance between the detection portion and the stem can vary (see column 11, lines 22-56

With regard to claim 27 and 59, Tyagi teaches that intact duplex probes are not detected (see column 5, lines 40-43).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-9, 11-34 and 40-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi et al (U.S. Patent 5,925,517) in view of Lizardi et al (WO 97/19193).

Tyagi (U.S. Patent 5,925,517) teaches a method of detecting target nucleic acid sequences (see abstract), the method comprising:

(a) bringing into contact one or more target samples and one or more structured probes (see columns 31-32, Example VI), and incubating under conditions that promote hybridization between target nucleic acid sequences in the target samples and the structured probes (see column 32, lines 7-13 and column 15, lines 1-23), wherein each structured probe is bifunctional (see figures 3 and 4), wherein one function is as a probe to a target nucleic acid sequence (see figures 3 and 4, and column 32, lines 30-40) and the other function is a detection function, wherein the detection function is not possible unless the probe hybridizes to the target nucleic acid sequence (see figures 3 and 4 and lines 30-40 and column 5, lines 27-67)

wherein each structured probe has a first end and a second end (see figures 3 and 4), wherein each structured probe comprises at least two complementary portions, a target probe portion (see figures 3 and 4 and column 5, lines 27-43 and columns 9-11) and a detection portion (see figures 3 and 4 and column 5, lines 27-43 and columns 9-11), wherein the two or more complementary portions comprise a first complementary portion and a second complementary portion, wherein two or more of the complementary portions form a duplex region (see figures 3 and 4) wherein formation of the duplex region forms a loop (see figures 3 and 4), wherein at least a portion of the

target probe portion is in the loop (see figures 3 and 4 and column 5, lines 27-43 and columns 9-11), wherein hybridization of the target probe portion to the target nucleic acid sequence disrupts the duplex region (see figures 3 and 4 and column 5, lines 27-43 and columns 9-11 and column 32, lines 30-40),

(b) detecting the structured probes (see column 32, lines 20-65),

wherein prior to detection, the structured probes are treated to alter or eliminate unhybridized probes wherein only probes with intact duplex regions are altered or eliminated by treatment of the structured probes, wherein altered and eliminated probes are not detected (see column 21, lines 51-55, where detection can be performed by polyacrylamide gel electrophoresis, which will separate hybridized probes from unhybridized probes). Further, Tyagi teaches the use of low stringency washing of solid supports such as Southern blots (see column 21, line 59 to column 22, line 13).

With regard to claim 2, 8 and 9, Tyagi teaches that the probe may have a single stranded overhang (see column 19, lines 13-15) wherein the probes are treated with the amplification (see column 20, lines 40-56).

With regard to claim 3, as above, Tyagi teaches that the probe may have a single strand overhang (see column 19, lines 13-15) and the functional limitation that the probe cannot prime is met by the 5' end, since the 5' end cannot prime amplification by itself.

With regard to claims 5-7, 15-18, 30-34, 44-47, Tyagi teaches formation of probes tethered to a solid support (see column 37, lines 15-40 and figure 10).

With regard to claims 20, 42 and 43, Tyagi teaches the use of low stringency washing of solid supports such as Southern blots (see column 21, line 59 to column 22, line 13).

With regard to claims 21-26, and 28, Tyagi teaches that the parameters of distance between the detection portion and the stem can vary (see column 11, lines 22-56

With regard to claim 27, 43 and 59, Tyagi teaches that intact duplex probes are not detected (see column 5, lines 40-43).

Tyagi does not teach use of a rolling circle primer segment for detection of the target.

Lizardi teaches detection methods in which a rolling circle amplification primer is used for the detection (see abstract and figure 25) (regarding claim 40). Lizardi expressly teaches that the molecular beacon probes of Tyagi can be used as detection probes (see page 18).

With regard to claim 41, Lizardi further teaches a method of bringing amplification target circles into contact with a probe and incubating under conditions that promote hybridization of the amplification target circles and the probes (see page 32, paragraph 2 and figure 25B), and incubating the amplification target circles and probes under conditions that promote replication of the amplification target circles (see page 32 and

figure 25B) wherein replication of the amplification target circles results in the formation of tandem sequence DNA (see page 32).

With regard to claim 4, Lizardi teaches the addition of chain terminating nucleotides during extension (see page 93, for example).

With regard to claims 11-14, 19, 42, Lizardi teaches removal of excess OCPs using an exonuclease that is double strand specific (see page 73).

With regard to claim 29, Lizardi expressly teaches that the molecular beacon probes of Tyagi can be used as detection probes (see page 18) and therefore will not disrupt the amplification.

With regard to claims 44-47, 52-55, Lizardi teaches attachment of the probes to a solid support in an array format (see page 19).

With regard to claim 48, 50, 51, 56, 57, 58, Lizardi teaches glass solid slide supports (see page 30) which are a sort of film composed of particles or polymers.

With regard to claim 49, Lizardi teaches that the dots can be variable in sized and therefore in separation distance (see page 30).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the probes of Tyagi with the Rolling Circle Amplification of Lizardi since Lizardi states "A particularly preferred detection probe is a molecular beacon. Molecular beacons are detection probes labeled with fluorescent moieties where the fluorescent moieties fluoresce only when the detection probe is hybridized (Tyagi and Kramer, Nature Biotechnology 14:303-308(1996) (see page 18)".

An ordinary practitioner would have been motivated to use the probes of Tyagi in the Lizardi method since Lizardi expressly notes that these are preferred probes which will efficiently detect only upon hybridization, which reduces background and improves sensitivity.

7. Claims 10 and 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi et al (U.S. Patent 5,925,517) in view of Lizardi et al (WO 97/19193) and further in view of Lizardi (U.S. Patent 6,316,229).

Tyagi et al (U.S. Patent 5,925,517) in view of Lizardi et al (WO 97/19193) teach the limitations of claims 1-9, 11-34 and 40-59 as discussed above. Tyagi et al (U.S. Patent 5,925,517) in view of Lizardi et al (WO 97/19193) do not teach formation of probes where there is a 5' to 5' junction between the detection portion and the target probe portion.

Lizardi (U.S. Patent 6,316,229) teaches an example of a bipartite rolling circle amplification primer (see figure 30 and column 8, lines 45-63) where the probe and target regions are linked by a 5' to 5' junction, which results in probes that are oriented 5' to 3' relative to each end (see figure 30 and column 8, lines 45-63, also see columns 11-12).

With regard to claim 10, Lizardi (U.S. Patent 6,316,229) teaches the use of terminators at one end, which prevents RCA function (see column 66-67)

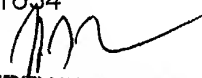
It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the bipartite primers of Lizardi (U.S. Patent 6,316,229) in the rolling circle amplification method of Tyagi et al (U.S. Patent

5,925,517) in view of Lizardi et al (WO 97/19193) since Lizardi (U.S. Patent 6,316,229) states "BP-RCA is useful, for example, for determining which target sequences are present in a nucleic acid sample, or for determining which samples contain a target sequence. The former can be accomplished, for example, by using a variety of probe sequences, each complementary to a different target sequence of interest, and different ATCs designed to be primed by only one of the primer sequences (present in a probe/primer) (see column 9, lines 39-46)." An ordinary practitioner would have been motivated to use the bipartite primers of Lizardi (U.S. Patent 6,316,229) in the method of Tyagi et al (U.S. Patent 5,925,517) in view of Lizardi et al (WO 97/19193) in order to permit detection in a simpler setup of multiple different targets as discussed by Lizardi (U.S. Patent 6,316,229).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634


JEFFREY FREDMAN
PRIMARY EXAMINER